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Clinical outcomes of endocrine and other disorders induced by immune checkpoint inhibitors in Japanese patients

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The purpose of this study was to analyze the efficacy of treatment and survival after administration of immune checkpoint inhibitor (ICI) in Japanese patients and had endocrine-related and/or other immune-related adverse events (irAEs), as well as irAEs in multiple organs. This is a single-center, retrospective, observational study of 571 Japanese patients treated with ICI at our hospital. We evaluated the occurrence of Grade 3 or higher irAEs and the life expectancy and treatment efficacy after ICI administration. Endocrine-related irAE (E-irAE), other irAE (O-irAE), endocrine-related and other irAE (EO-irAE), and multiple endocrine-related irAE (ME-irAE) were evaluated in groups. 80.8% of patients had an irAE, with the highest incidence of irAE with ipilimumab plus PD-1 inhibitor, followed by atezolizumab 59.0%, pembrolizumab 53.7%, avelumab 50.0%, and nivolumab 47.3%, Durvamumab 26.7% followed; Kaplan-Meier survival curves showed higher survival rates in patients with irAE compared to non-irAE, and higher survival rates in EO-irAE and ME-irAE compared to E-irAE and O-irAE ($p < 0.001$). The COX proportional hazard ratios for overall survival were E-irAE 0.611 (0.480–0.772), O-irAE 0.758 (0.597–0.957), EO-irAE 0.622 (0.466–0.819) and ME-irAE 0.463 when non-irAE was set at 1.000 (0.257–0.775). When grade 3 or higher irAEs appeared, regardless of their type, there was a trend toward higher survival and post-treatment remission rates after ICI administration. In addition to this, patients with irAEs in multiple endocrine tissues and patients with irAEs in both endocrine and other organs had a better response to treatment after ICI administration.

Keywords Immune-related adverse events, Immune check point inhibitors, Endocrine disorder, Retrospective study

Immune checkpoint inhibitors (ICIs) cause a variety of immune-related adverse events (irAEs) in a variety of organs such as the lung, colon, skin, and endocrine organs[1]. The mechanism by which irAEs occur is not entirely clear, but it is thought to be bystander effects of T cells activated by ICIs[2,3]. Endocrine- and skin-related irAEs were reported to correlate with improved response to ICIs and survival from some malignancies[4]. Improved clinical outcome after ICI administration has been reported in patients with irAEs in multiple organs compared to those with irAEs in a single organ[5]. We conducted a single-center retrospective study of 466 Japanese patients treated with ICIs at Kawasaki Medical School Hospital. Our results showed that survival was significantly higher in patients with endocrine-related irAEs than in those without them[6]. We also reported that the severity of thyroid-related irAEs correlated with the response rate to ICIs[7]. Other studies have reported that ICI-induced thyroid disorders are significantly correlated with survival after ICI administration[8–10]. It has also been reported that the occurrence of adrenal-related irAEs is associated with a favorable clinical outcome[11]. Endocrine-related irAEs, especially thyroid disorders, may be a surrogate marker for predicting treatment response to ICIs. On the other hand, most studies to date have focused on single organ irAEs, and few studies have evaluated which combination of multiple irAEs makes a difference in treatment efficacy when multiple irAEs are induced. In this study, we aimed to analyze treatment efficacy and survival after administration of ICIs in Japanese patients at our hospital and had endocrine-related and/or other irAEs, as well as irAEs in several organs.

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Materials and methods

Study population and patient preparation

This is a single-center, retrospective, observational study of a total of 571 patients treated with ICIs at Kawasaki Medical School Hospital from September 1, 2014 to March 31, 2023. Among the 571 patients who were treated with ICIs at our hospital during this period, 273 had no irAE (non-irAE), 109 had irAE only in a single endocrine organ (endocrine-related irAE: E-irAE), 108 had irAE in other organs than endocrine organs (other irAE: O-irAE), and 67 patients had both endocrine-related and other irAE (endocrine-related and other irAE: EO-irAE). Fifteen patients had multiple endocrine-associated irAE (multiple endocrine-related irAE: ME-irAE). Among these patients, 12 had hypothyroidism combined with isolated ACTH deficiency, 2 had hypothyroidism combined with insulin-dependent diabetes mellitus, and 1 had hypothyroidism combined with Addison's disease. The definition of each irAE is given in a separate section. As previously reported[7], ICIs used in our hospital are cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors (ipilimumab), programmed cell death protein 1 (PD-1) inhibitors (nivolumab and pembrolizumab), and programmed cell death protein 1 ligand 1 (PD-L1) inhibitors (atezolizumab, durvalumab, and avelumab). The study protocol, including the use of opt-out informed consent, was approved by the Kawasaki Medical School Institutional Review Board (No. 5726-01). Due to the retrospective nature of the study, the Kawasaki Medical School Institutional Review Board waived the need of obtaining informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Diagnosis of each irAE

The severity of each irAE is based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://www.jcog.jp/doctor/tool/CTCAEv5J_20220901_v25_1.pdf). In this study, E-irAE was defined as thyroid dysfunction, hypoadrenocorticism, hypopituitarism, insulin-dependent diabetes mellitus, and abnormal parathyroid function. Hypoadrenocorticism, hypopituitarism, and insulin-dependent diabetes mellitus were defined as CTCAE Grade 3 or higher. As for thyroid dysfunction, we determined that only thyroid dysfunction of Grade 1 or higher was considered to have endocrine-related irAE, since our previous studies have reported that even Grade 1 improves the prognosis after ICI administration[7]. O-irAE was defined as irAEs other than endocrine-related irAEs that were CTCAE Grade 3 or higher. O-irAEs were evaluated separately in interstitial pneumonia, biliary tract injury, enteritis, skin injury, renal tubular injury, and other irAEs such as bone marrow suppression ($n=16$), peripheral neuropathy ($n=15$), hepatic disorder ($n=11$), rhabdomyolysis ($n=4$), autoimmune pancreatitis ($n=2$), nephrotic syndrome ($n=2$), uveitis ($n=1$) and herpes cornea ($n=1$).

Statistical analysis

Data are expressed as median and interquartile range. The primary endpoint was to assess the correlation between the severity of E-irAE, O-irAE, EO-irAE, and ME-irAE and the efficacy of immunotherapy. The secondary endpoint was to determine the clinical characteristics of irAEs in each organ. This study was conducted in all patients who received ICI at our hospital. Data collection was based on a uniform protocol, and data extraction of medical record information was performed by independent data management department personnel. Only those cases for which it was confirmed in the medical record that a medical response had been taken were treated as irAE. The remission rate by RECIST (Response Evaluation Criteria in Solid Tumors) criteria and the prevalence of malignancy by stage after administration of ICIs in each group were evaluated by the chi-square test. The frequency of irAEs by each ICI was also evaluated with a chi-square test. The Mann-Whitney U test was used to evaluate the difference in observation period depending on the presence or absence of each irAE. The Kruskal-Wallis test was used to analyze the age of each group and the number of ICI administration, and the Dunn test was used as a post hoc test. Kaplan-Meier survival curves were generated for each group from the first dose of ICI to death or, if alive, to March 31, 2024, as overall survival (OS), which was evaluated with a log-rank test. Progression-free survival (PFS) was defined as the period from the first administration of ICI until the time when progressive disease (PD) was judged by clinical or laboratory findings, or until March 31, 2024 if the patient was alive, and was evaluated using the log-rank test. Patients who were transferred during the treatment were calculated as survivors, and the observation period was censored at the date of the last visit. If the date of death was still known after transfer, the date of death was used as the observation end date. The failure rate plots for the Kaplan-Meier curves for OS and PFS for each group are shown in Supplementary Fig. 1. Kaplan-Meier curves were analyzed by grouping each type of irAE for all participants in this study and for participants who survived for at least 1 year after ICI administration. Kaplan-Meier curves were created for non-small cell lung cancer (NSCLC), gastrointestinal tumors (GIT), hepatocellular carcinoma (HCC), otolaryngological tumors (OLT), urothelial carcinoma (UTC), malignant melanoma (MM), renal cell carcinoma (RCC), and small cell lung cancer (SCLC), which included more than 20 participants each, as an evaluation of survival time by malignancy. Dummy variables were assigned to E-irAE, O-irAE, EO-irAE, and ME-irAE, respectively, to calculate the hazard ratio of each irAE to OS. To adjust for potential confounding factors that may affect the PFS, the COX proportional hazards model included age, sex, type of irAE, ICI used, and history of chemotherapy and radiotherapy as covariates in the model. The selection of confounding factors was based on variables that met $p<0.05$ in univariate analysis and variables considered to be clinically important, and VIF was used to check for multicollinearity. The VIF of the covariates was all less than 3 (Supplementary Fig. 2). To calculate the proportional hazard ratio by age, we assigned a dummy variable to subjects stratified by age (under 50 years old, 60s, 70s, and over 80 years old), and calculated the respective hazard ratio for subjects under 50 years old. JMP version 17.0.0 (SAS Institute Inc., North Carolina, USA) was used for all statistical analyses, and Microsoft Excel for Mac version 16.83 (Microsoft Co., WA, USA) was used to create tables.

Results

Clinical characteristics of the participants in this study

The age of this study subjects at the time of ICI administration was 70 years old (63–75), with no difference in age between the presence and absence of irAE ($p=0.35$, Fig. 1A). Overall, 71.6% were male, and there was no sex difference between the subjects with and without irAE ($p=0.84$). The number of times ICI was administered for each irAE is shown in Fig. 1B. ICI was administered 5 times (2–11 times) in non-irAE group, while 10 times (6–21 times) in E-irAE and 23 times (6–37 times) in ME-irAE, both of which were significantly more frequent compared to non-irAE ($p<0.001$). Stage of malignancy was Stage I in 26 patients, Stage II in 46 patients, Stage III in 148 patients, and Stage IV in 347 patients, with no significant difference between patients with and without irAEs ($p=0.40$, Fig. 1C). The incidence of irAEs and primary sites for each ICI are shown in Table 1; Fig. 1D. The highest rate of any irAE occurred with the combination of ipilimumab and PD-1 inhibitor at 69.2%, followed by atezolizumab, avelumab, pembrolizumab, nivolumab, and durvalumab. Among the E-irAEs, the most frequent were thyroid-related irAEs. O-irAEs had the highest rates of interstitial pneumonia for nivolumab, pembrolizumab and durvalumab. The incidence of EO-irAE were higher for ipilimumab in combination with PD-1 inhibitors, as well as pembrolizumab and nivolumab. For PD-1 inhibitors overall, the incidence of E-irAEs and O-irAEs were 32.5% and 29.7%, respectively. For PD-L1 inhibitors overall, the incidence of E-irAEs and O-irAEs were 32.5% and 33.3%, respectively.

Survival and treatment efficacy after ICI administration for each irAE

Survival curves after administration of ICIs in each group are shown in Fig. 2. Compared to the non-irAE group, the groups with any irAE had better OS and PFS, and the EO-irAE and ME-irAE groups had even better survival rates than the O-irAE and E-irAE groups (Fig. 2A, B; Table 2). The mean observation period for each group in this study is shown in Fig. 3A. The mean observation period was significantly longer in E-irAE, EO-irAE, and ME-irAE group compared to non-irAE ($p<0.001$, $p=0.0041$, and $p<0.001$, respectively). And ME-irAE group had a significantly longer mean observation period than O-irAE and E-irAE ($p=0.0020$, $p=0.036$). The mean observation period for each group in this study is shown in Fig. 3A. The mean observation period was significantly longer in E-irAE, EO-irAE, and ME-irAE group compared to non-irAE ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). And ME-irAE group had a significantly longer mean observation period than O-irAE and E-irAE ($p<0.001$, $p=0.030$). Survival ratio three years after ICI administration was 28.4% in non-irAE group, 37.9% in O-irAE, 42.0% in E-irAE, 53.6% in EO-irAE, and 66.7% in ME-irAE ($p<0.001$, Fig. 3B). Next, Fig. 3C shows the results of the retrospective evaluation of the remission rate from ICI administration to the

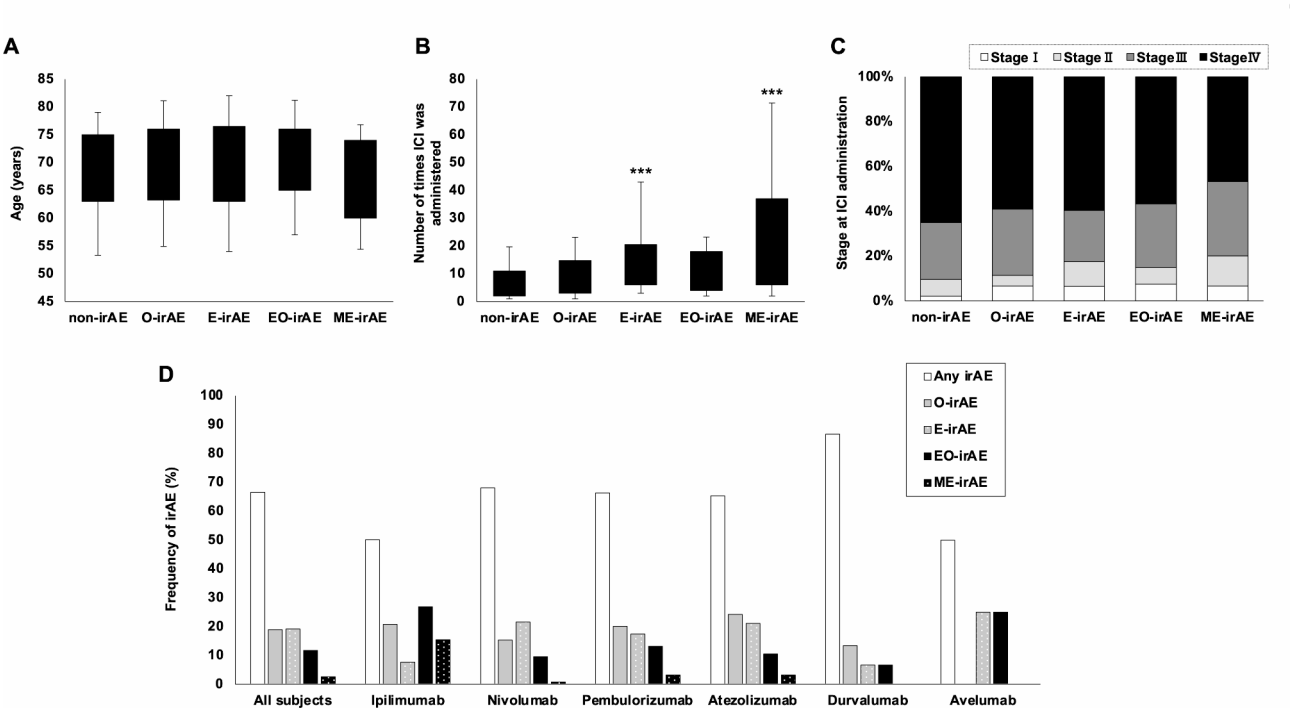

Fig. 1. (**A**) Age at the first ICI administration. (**B**) Number of times ICI was administered during the observation period. (**C**) Stage of malignancy at the time of the first dose of ICI. (**D**) Frequency of irAEs for each ICI used. Non-irAE, subjects without irAE ($n=285$); E-irAE, those having only endocrine-related irAE ($n=112$); O-irAE, those having other irAE ($n=103$), EO-irAE, those having both endocrine-related and other irAE ($n=56$); ME-irAE, those having multiple endocrine-related irAE ($n=15$). Data for age and number of times ICI was administered represent interquartile range (IQR), and error bars represent 90% tiles. Kruskal-Wallis test or chi-square test was used for analysis. ***$p<0.001$ vs. non-irAE.

	Ipilimumab and PD-1 inhibitors ($n=26$)	Nivolumab ($n=241$)	Pembrolizumab ($n=190$)	Atezolizumab ($n=95$)	Dulbumumab ($n=15$)	Avelumab ($n=4$)
Any irAEs (%)	80.8	47.3	53.7	59.0	26.7	50.0
Endocrine-related irAEs (%)	50.0	32.0	33.7	34.7	13.3	50.0
Multiple endocrine-related irAEs (%)	15.4	0.8	3.2	3.2	0	0
Thyroid-related irAEs (%)	50.0	28.6	29.5	31.6	13.3	50.0
Adrenal-related irAEs (%)	15.4	2.1	3.7	6.3	0	25.0
Pituitary-related irAEs (%)	15.4	1.2	4.2	3.2	0	25.0
Insulin-dependent diabetes (%)	0	0.8	1.6	0	0	0
Other irAEs (%)	47.7	24.9	33.2	34.7	20.0	25.0
Interstitial pneumonia (%)	19.2	12.0	12.6	4.2	13.3	0
Biliary tract disorders (%)	3.9	0.8	3.7	1.1	0	0
Enterocolitis (%)	19.2	2.9	5.3	8.4	0	0
Skin disorders (%)	15.4	5.8	7.9	4.2	0	25.0
Renal tubular disorders (%)	7.7	0.4	2.1	3.2	6.7	0
Other irAEs except for above (%)	15.4	6.2	9.0	15.8	6.7	0
Endocrine-related and other irAE complications (%)	26.9	9.5	13.2	10.5	6.7	25
Percentage of primary disease						
Non-small cell lung cancer ($n=179$) (%)	4.6	42.2	33.3	16.6	8.4	0
Gastrointestinal Tumors ($n=144$) (%)	0	91.7	8.3	0	0	0
Hepatocellular carcinoma ($n=44$) (%)	0	0	0	100	0	0
Otolaryngological tumors ($n=43$) (%)	3.9	62.8	37.2	0	0	0
Urothelial cancer ($n=42$) (%)	2.4	0	92.9	0	0	4.8
Malignant melanoma ($n=35$) (%)	28.6	40.0	31.4	0	0	0
Renal cell cancer ($n=27$) (%)	33.3	40.7	18.5	0	0	7.4
Small cell lung cancer ($n=23$)	0	0	0	100	0	0
Other tumors ($n=27$) (%)	3.7	33.3	48.1	14.8	0	0
Cancer of unknown primary ($n=7$) (%)	0	85.7	14.3	0	0	0

Table 1. Prevalence of endocrine-related and other irAEs after treatment with various immune checkpoint inhibitors and percentage of primary disease. irAEs; immune-related adverse events, PD-1; programmed cell death protein 1, PD-L1; programmed cell death protein 1 ligand 1. Other tumors included the following primary tumors; hematologic tumors ($n=9$), breast cancer ($n=9$), female organ related tumors ($n=5$), and malignant pleural mesothelioma ($n=4$). The chi-square test was used for analysis.

final time point of the ICI administration period. Next, Fig. 3C shows the results of a retrospective evaluation of the remission rate from ICI administration to the final time point of the ICI treatment period. The rate of partial remission (PR) or complete remission (CR) in non-irAE group was 18.0%, which was lower compared to 34.3% in O-irAE, 45.0% in E-irAE, 49.5% in EO-irAE, and 66.7% in ME-irAE ($p<0.001$). The percentages of stable disease (SD) were 16.9% in non-irAE group, 22.2% in O-irAE, 20.2% in E-irAE, 29.9% in EO-irAE, and 33.3% in ME-irAE. In contrast to the above, the percentage of PD was highest in non-irAE at 65.1%, followed by O-irAE at 43.5%, E-irAE at 34.9%, EO-irAE at 22.4%, and ME-irAE at 13.3%.

Survival of participants who survived for more than one year after ICI administration

Since irAEs caused by ICI generally develop within one year in most cases, a landmark analysis was conducted in the 301 patients who survived for more than one year. The PFS of participants who survived for more than one year was significantly longer in the EO-irAE and ME-irAE groups than in the non-irAE group (Figs. 4A and 5A). On the other hand, there was no significant difference in OS by type of irAE in participants who survived for more than 1 year (Figs. 4B and 5B). The proportion of patients who achieved PR or CR after ICI treatment was 40.2% for non-irAE, 42.2% for O-irAE, 64.3% for E-irAE, 50.0% for EO-irAE, and 61.5% for ME-irAE. The proportion of patients who developed PD after ICI administration was 48.0% for non-irAE, and was lower for O-irAE (37.5%), E-irAE (20%), EO-irAE (19.2%), and ME-irAE (15.4%) (Fig. 5C).

Differences in observation periods for each type of irAE

Next, we evaluated in more detail the differences in observation period by type of irAEs (Table 3). As the results, among the endocrine-related irAEs, subjects with thyroid-related irAEs, adrenal-related irAEs, pituitary-related irAEs, and multiple endocrine-related irAEs tended to have longer observation period ($p<0.001$, respectively). As for other irAEs, observation period was significantly longer in subjects with interstitial pneumonia, skin disorder and other irAEs except for above ($p=0.030$, $p=0.023$ and $p=0.0097$, respectively). There was no difference in observation period in the participants of this study according to the presence or absence of irAEs for insulin-dependent diabetes mellitus, biliary tract disorders, enterocolitis, and renal and urinary tract disorders.

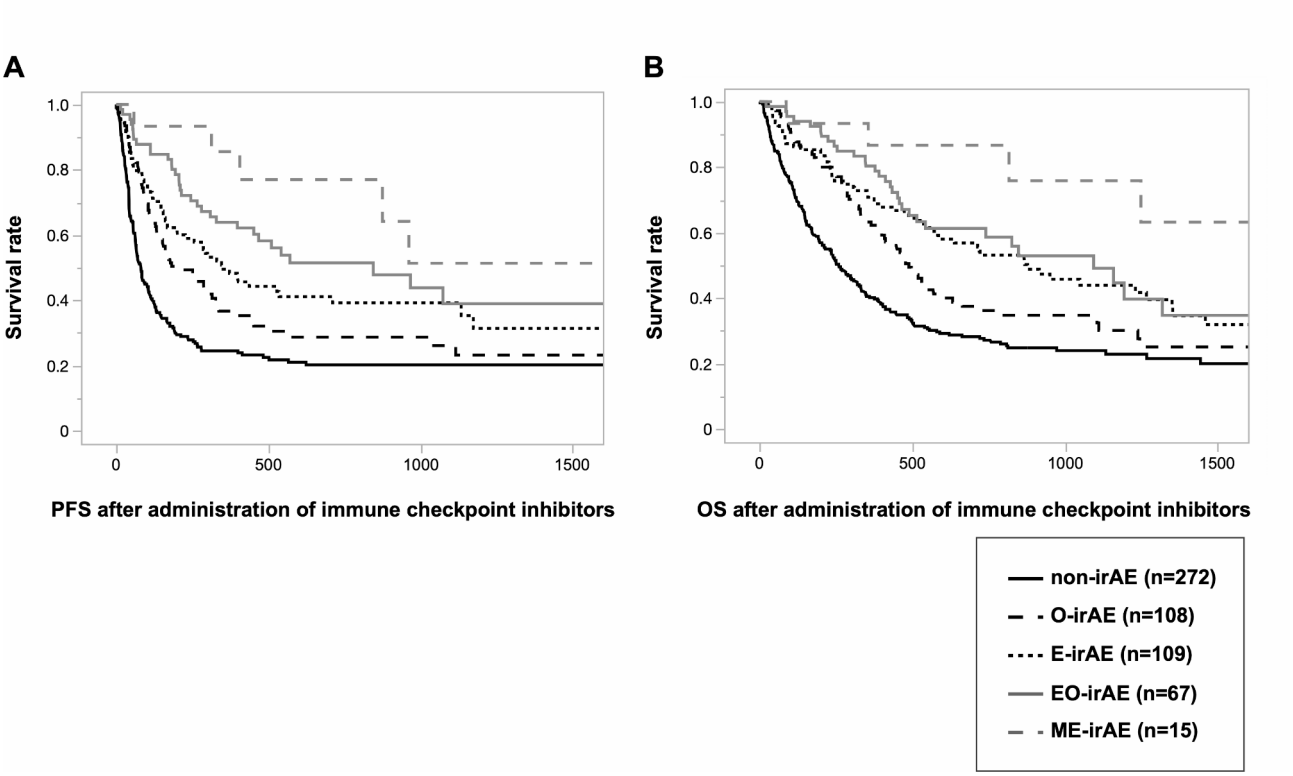

Fig. 2. Kaplan-Meier survival curves by irAE occurring in ICI treatment were generated and analyzed using the log-rank test. (**A**) Progressive-free survival (PFS) after administration of ICIs. (**B**) Overall survival (OS) after administration of ICIs. Non-irAE ($n=272$); E-irAE, endocrine-related irAE alone ($n=108$); O-irAE, other irAEs ($n=109$), EO-irAE, both endocrine-related and other irAEs ($n=67$); ME-irAE, multiple endocrine-related irAEs ($n=15$).

PFS after administration of ICIs	0 days	30 days	60 days	90 days	180 days	360 days	720 days	1080 days	1420 days
Non-irAE (%, (n))	100 (272)	80.3 (218)	60.6 (163)	46.1 (119)	32.0 (67)	24.5 (42)	20.2 (24)	20.2 (14)	20.2 (9)
O-irAE (%, (n))	100 (108)	93.5 (101)	83.1 (88)	73.5 (76)	51.4 (50)	36.7 (28)	28.7 (16)	26.1 (10)	23.2 (6)
E-irAE (%, (n))	100 (109)	92.7 (102)	79.8 (87)	76.9 (86)	62.3 (61)	49.5 (40)	39.2 (22)	39.2 (11)	31.4 (8)
EO-irAE (%, (n))	100 (67)	97.0 (65)	89.3 (59)	87.8 (58)	83.2 (55)	63.9 (39)	51.5 (16)	38.9 (9)	38.9 (6)
ME-irAE (%, (n)	100 (15)	100 (15)	93.3 (15)	93.3 (15)	93.3 (15)	85.6 (11)	77.0 (9)	51.3 (5)	51.3 (3)
OS after administration of ICIs	**0 days**	**30 days**	**60 days**	**90 days**	**180 days**	**360 days**	**720 days**	**1080 days**	**1420 days**
Non-irAE (%, (n))	100 (272)	92.3 (252)	84.1 (229)	77.1 (208)	59.2 (154)	40.1 (103)	27.7 (53)	24.0 (24)	20.0 (14)
O-irAE (%, (n))	100 (108)	98.2 (107)	96.3 (104)	92.5 (98)	82.9 (87)	63.2 (65)	37.5 (30)	34.7 (16)	25.1 (10)
E-irAE (%, (n))	100 (109)	98.2 (108)	92.7 (102)	87.2 (96)	85.3 (92)	70.8 (72)	53.1 (45)	43.9 (25)	34.6 (14)
EO-irAE (%, (n))	100 (67)	100 (67)	98.5 (66)	95.5 (64)	92.5 (62)	80.3 (54)	61.3 (24)	52.9 (16)	34.7 (8)
ME-irAE (%, (n)	100 (15)	100 (15)	100 (15)	93.3 (15)	93.3 (15)	86.7 (14)	86.7 (11)	75.8 (8)	63.2 (7)

Table 2. Survival rate at each time point on the Kaplan-Meier curve. PFS; Progression-free survival, ICI; immune-checkpoint inhibitor, irAEs; immune-related adverse events, OS; overall survival. The log-rank test was used for the analysis.

Hazard ratio (HR) of each irAE to overall survival

To evaluate the occurrence of each irAE and its impact on overall survival (OS), HR was calculated and the results are shown in Table 4. When the HR of non-irAE to OS was set at 1.000, the HR was lower for O-irAE, EO-irAE, E-irAE, and ME-irAE, in that order. The HR were higher in subjects aged 70–79 years and those aged 80 years or older compared to those aged < 50 years at the time of administration. There were no significant trends between each factor (sex, ICI used, prior chemotherapy and radiation therapy) and OS.

Next, the hazard ratios of each irAE to OS after ICI treatment for each irAE were evaluated by primary disease, and the results are shown in Table 5. The HR for ME-irAE was significantly lower than that for non-irAE in non-small cell lung cancer and small cell lung cancer. The HRs of E-irAE, O-irAE, and EO-irAE were

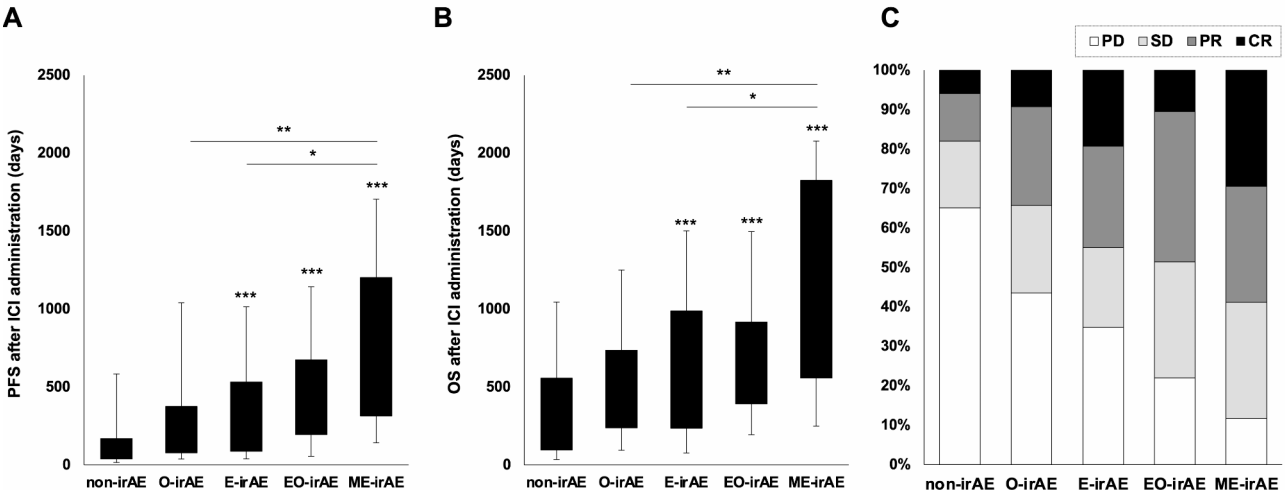

Fig. 3. (**A**) Progression-free survival (PFS) from first dose of ICI to death or transfer to another physician or to March 31, 2024. (**B**) Overall survival (OS) from first dose of ICI to death or transfer to another physician or to March 31, 2024. Data presented interquartile range (IQR) and error bars represent 90% tiles. Kruskal-Wallis test was used to analyze the results. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ vs. non-irAE. (**C**) Remission rate from ICI administration to the time of change of anticancer therapy or last check. Remission rates were analyzed using the chi-square test. Non-irAE ($n = 272$); E-irAE, endocrine-related irAE alone ($n = 108$); O-irAE, other irAEs ($n = 109$), EO-irAE, both endocrine-related and other irAEs ($n = 67$); ME-irAE, multiple endocrine-related irAEs ($n = 15$). PD; progressive disease, SD; stable disease, PR; partial remission, CR; complete remission.

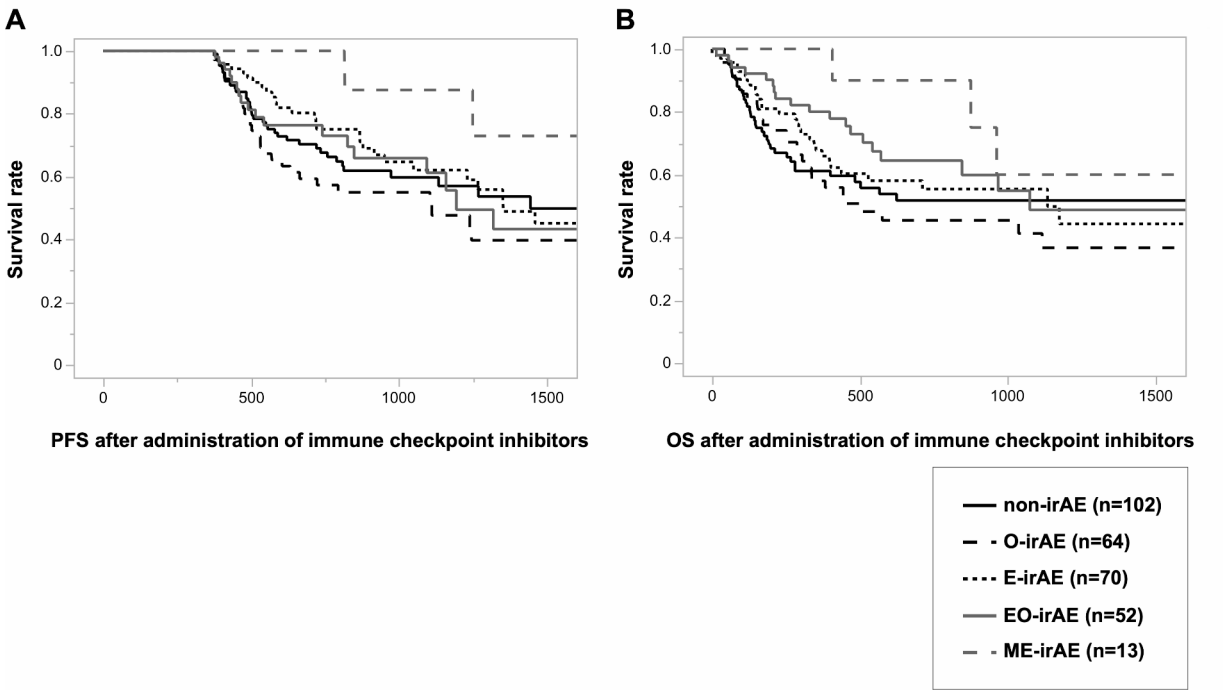

Fig. 4. Only participants who survived for more than one year after ICI administration were included, and a Kaplan-Meier survival curve was created and analyzed using the log-rank test for irAEs that occurred during ICI treatment. (**A**) Progressive-free survival (PFS) after administration of ICIs. (**B**) Overall survival (OS) after administration of ICIs. Non-irAE ($n = 102$); E-irAE, endocrine-related irAE alone ($n = 64$); O-irAE, other irAEs ($n = 70$), EO-irAE, both endocrine-related and other irAEs ($n = 52$); ME-irAE, multiple endocrine-related irAEs ($n = 13$).

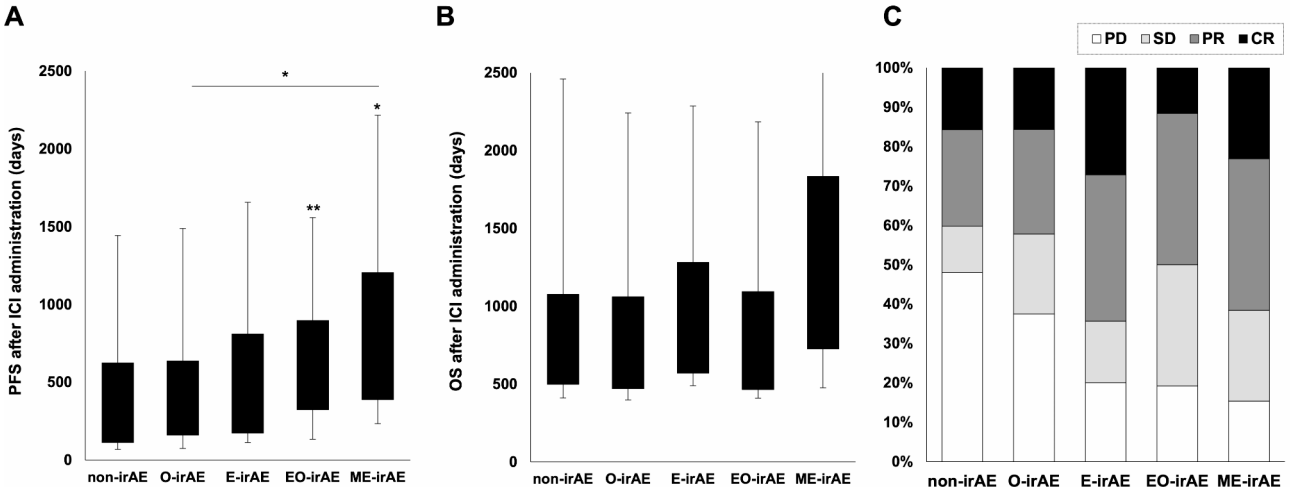

Fig. 5. (**A**) Progression-free survival (PFS) from first dose of ICI to death or transfer to another physician or to March 31, 2024. (**B**) Overall survival (OS) from first dose of ICI to death or transfer to another physician or to March 31, 2024. Data presented interquartile range (IQR) and error bars represent 90% tiles. The analysis was conducted on participants who survived for more than one year after ICI administration. Kruskal-Wallis test was used to analyze the results. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ vs. non-irAE. (**C**) Remission rate from ICI administration to the time of change of anticancer therapy or last check. Remission rates were analyzed using the chi-square test. Non-irAE ($n = 102$); E-irAE, endocrine-related irAE alone ($n = 64$); O-irAE, other irAEs ($n = 70$), EO-irAE, both endocrine-related and other irAEs ($n = 52$); ME-irAE, multiple endocrine-related irAEs ($n = 13$). PD, progressive disease; SD, stable disease; PR, partial remission; CR, complete remission.

significantly lower than those of non-irAE in RCC and UTC. In OLT, only the HR of EO-irAE tended to be lower than that of non-irAE. In GIT, HCC, and MM, there was no difference among several irAE groups.

Characteristics of the observation period and each irAEs for each malignancy

We evaluated the clinical outcomes and irAEs after ICI administration in participants with each malignancy. The Kaplan-Meier curves for each malignancy are shown in Fig. 6A. The observation period was longest for MM, RCC, HCC, NSCLC, UTC, SCLC, GIT, and OLT in that order ($p < 0.0001$, Fig. 6B). Participants who achieved CR or PR after ICI administration were most common in GIT (55.3%), R CC (51.9%), SCLC (39.1%), MM (34.3%), HCC (34.1%), NSCLC (31.9%), UTC (23.8%), and ORT (11.6%) ($p < 0.0001$, Fig. 6C). The incidence of irAEs in each malignancy is shown in Fig. 6D. The incidence of irAEs was high in RCC and HCC, and low in ORT, SCLC, and UTC. The relationship between irAEs and remission rates in each malignancy was evaluated. There was a significant correlation between each irAE and remission rate in patients with NSCLC, GIT, and OLT ($p < 0.0001$, $p = 0.029$, $p = 0.0062$, Supplementary Fig. 3).

The relationship between radiation therapy and each irAEs

Finally, we analysed the relationship between radiotherapy and each irAEs. Of the participants, 144 had a history of radiotherapy and 427 did not. The incidence of any irAE was 43.1% among participants with a history of radiotherapy and 55.5% among those without a history of radiotherapy, with no statistical difference ($p = 0.072$). There was no statistical difference in the incidence of irAEs with or without radiotherapy for each type of malignant tumor (Supplementary Fig. 4).

Discussion

These retrospective data showed that patients who developed endocrine-related irAEs after ICI treatment had significantly higher survival rates than those who developed other irAEs. Furthermore, we found that the remission rate with ICI treatment was higher in patients who developed irAE in multiple organs or multiple endocrine organs. Although irAEs have been drawing much attention recently, there were few reports showing which combination of multiple irAEs (endocrine-related and/or other irAEs) makes a difference in treatment efficacy of ICIs and prognosis of various disorders. To the best of our knowledge, this is the first report clarifying this point. Therefore, we think that the data obtained in this study would be informative and useful from the clinical and academic point of view.

Endocrine-related irAE is associated with treatment prognosis. Thyroid-related irAEs are the most frequent irAEs after ICI administration[10]. Thyroid-related irAEs are associated with thyroid peroxidase and thyroid

	Overall survival (days)		
	With	Without	*P* value
Any irAEs	517 (269–923)	242 (96–556)	< 0.001
Endocrine-related irAE	569 (311–1021)	298 (115–597)	< 0.001
Multiple endocrine-related irAE	817 (557–1825)	296 (114–599)	< 0.001
Thyroid-related irAE	571 (312–993)	332 (131–653)	< 0.001
Adrenal-related irAE)	795 (423–1312)	389 (143–757)	< 0.001
Pituitary-related irAE	956 (452–1458)	389 (145–752)	< 0.001
Insulin-dependent diabetes	356 (246–1517)	397 (147–780)	0.34
Other irAEs	489 (322–889)	319 (115–740)	< 0.001
Interstitial pneumonia	532 (274–1030)	376 (134–768)	0.030
Biliary tract disorders	402 (148–788)	254 (120–543)	0.55
Enterocolitis	434 (269–1038)	397 (144–767)	0.16
Skin disorders	561 (390–987)	378 (142–759)	0.023
Renal tubular disorders	412 (378–612)	397 (146–788)	0.61
Other irAEs except for above	473 (397–916)	375 (138–768)	0.0097
Endocrine and other irAE complications	515 (391–916)	241 (95–556)	< 0.001

Table 3. Association between type of irAEs and overall survival. Data are presented as median (IQR). irAEs; immune-related adverse events. Other irAEs except for above included the following irAEs; bone marrow suppression (n=16), peripheral neuropathy (n=15), hepatic disorder (*n*=11), rhabdomyolysis (*n*=4), autoimmune pancreatitis (*n*=2), nephrotic syndrome (*n*=2), uveitis (*n*=1) and herpes cornea (*n*=1). The Mann-Whitney U test was used for analysis.

globulin antibodies and are caused by lymphocyte and cytokine infiltration into thyroid tissue[12,13]. The abundance of peripheral blood lymphocytes is also associated with the occurrence of irAEs and a good response to ICI[14]. Since thyroid-related irAEs are associated with the antitumor effect of ICIs, it has been suggested that they may be used as surrogate markers of clinical response. Correlation between thyroid-related irAEs and clinical outcome has been reported especially in patients with non-small cell carcinoma[15]. In a previous report[5], progression-free survival was significantly prolonged when several irAEs, including interstitial pneumonia, hepatitis, and skin disorders, were combined in addition to thyroid-related irAEs compared to a single irAE. In the present study, subjects with non-small cell lung cancer complicated by several irAEs had the longest observation period and highest post-treatment remission rates, which was consistent with previous studies. Interestingly, a similar trend was observed in subjects with renal-urinary tract and otorhinolaryngological tumors, where the clinical efficacy of ICI was superior in ME-irAE group compared to EO-irAE in many tumors. There are only a limited number of reports on the correlation between multi-organ irAEs and OS and PFS, and it is necessary to accumulate case numbers in various regions. Few reports are showing the differences in prognosis between patients with individual irAEs such as E-irAE and O-irAE, and patients with multiple irAEs, and the new regulations of this study have been presented. Further research will be needed in the future to clarify the reasons for the improved prognosis in patients with several irAEs.

In this study, the observation period was longer in subjects with adrenal-related irAE and pituitary-related irAE in addition to thyroid-related irAE. ICI-induced adrenal insufficiency was considered to be one of findings reflecting T-cell activation and correlated with the efficacy of ICI therapy in patients who developed adrenal insufficiency[16,17]. As a mechanism for pituitary-associated irAE, histopathologic analysis suggests that treatment with anti-CTLA-4 antibodies may cause anterior pituitary inflammation, especially in patients whose pituitary glands express high levels of CTLA-4 antigen[18]. The appearance of endocrine-associated irAEs reflected T-cell activation by ICIs, and patients with irAEs in multiple endocrine tissues could benefit from ICIs.

ICI-associated interstitial pneumonia has been reported as an irAE that can directly lead to decreased survival[19,20]. However, unlike previous studies, in this study, patients with Grade 3 or higher interstitial pneumonia had a longer overall survival and better response to ICI treatment. In our hospital, corticosteroid preparations are often administered at relatively early stage in patients with suspected interstitial pneumonia, and since a response rate of 70–80% can be expected with the administration of steroids in previous reports, regular follow-up may be beneficial for ICI-related interstitial pneumonia[21,22]. Skin disorders are frequent irAEs and are expected to be a factor to infer longer overall survival (OS) after ICI administration as observed in endocrine-related irAEs[23,24]. In the present study, patients with irAEs in the skin had significantly longer OS than those without irAEs. The effect of enteritis on OS has not been consistent in the previous studies[23], and there was no association between OS and enteritis in this study as well.

In this study, the characteristics of the hazard ratio due to the occurrence of irAEs differed depending on the type of malignancy. As shown in Table 5, in NSCLC, RCC, UTC, OLT, and SCLC, the HR for OS decreased when irAEs occurred in the endocrine organs or other organs. On the other hand, the occurrence of irAEs did not affect OS in GIT, HCC, and MM. Participants with GIT in this study had a shorter observation period and a lower incidence of irAEs compared to participants with other malignancies (Fig. 6B and D). On the

Parameter	Hazard ratio	95% CI
Age		
Under 50 years	1.000	
60–69 years	1.017	0.780–1.335
70–79 years	1.284	1.000–1.662
Over 80 years	1.428	1.019–1.993
Sex		
Male	1.000	
Female	1.023	0.796–1.199
Each irAE		
Non-irAE	1.000	
E-irAE	0.611	0.480–0.772
O-irAE	0.758	0.597–0.957
EO-irAE	0.622	0.466–0.819
ME-irAE	0.463	0.257–0.775
Immune checkpoint inhibitor		
Ipilimumab/PD-1 inhibitor	1.000	
PD-1 inhibitor	0.780	0.498–1.261
PD-L1 inhibitor	0.897	0.522–1.567
History of chemotherapy		
Without	1.000	
With	0.972	0.799–1.186
History of radiation therapy		
Without	1.000	
With	1.012	0.812–1.258

Table 4. Hazard ratios of each parameter to overall survival. Data are presented as median (IQR). 95%CI; 95% confidence interval, irAE; immune-related adverse events, E-irAE; endocrine-related irAE, O-irAE; other irAE, EO-irAE; endocrine-related and other irAE, ME-irAE; multiple endocrine-related irAE, PD-1; programmed cell death protein 1, PD-L1; programmed cell death protein 1 ligand 1. The hazard ratio was calculated using a dummy variable.

Primary disease	Non-irAE	E-irAE	O-irAE	EO-irAE	ME-irAE
Non-small cell lung cancer ($n=179$) (%)	1.000	0.515 (0.325–0.795)	0.766 (0.517–1.125)	0.551 (0.339–0.872)	0.340 (0.081–0.958)
Gastrointestinal tumors ($n=144$) (%)	1.000	0.695 (0.440–1.069)	0.636 (0.379–1.023)	0.757 (0.349–1.452)	0.539 (0.030–2.467)
Hepatocellular carcinoma ($n=44$) (%)	1.000	0.773 (0.303–2.028)	0.847 (0.292–2.425)	1.276 (0.478–3.390)	1.193 (0.176–5.008)
Otolaryngological tumors ($n=43$) (%)	1.000	0.421 (0.102–1.305)	0.340 (0.077–1.043)	0.342 (0.104–0.925)	-
Urothelial cancer ($n=42$) (%)	1.000	0.716 (0.259–1.822)	1.526 (0.318–5.374)	0.689 (0.103–2.673)	0.287 (0.013–2.332)
Malignant melanoma ($n=35$) (%)	1.000	0.991 (0.323–2.824)	0.937 (0.327–2.665)	1.036 (0.133–8.473)	0.991 (0.323–2.824)
Renal cell cancer ($n=27$) (%)	1.000	0.017 (0.001–0.200)	0.054 (0.004 – 0.001)	0.158 (0.028–0.888)	0.352 (0.056–1.776)
Small cell lung cancer ($n=23$)	1.000	1.181 (0.300–4.058)	2.199 (0.607–7.521)	-	0.041 (0.002–0.535)

Table 5. Hazard ratios of each irAE to overall survival by primary disease. Data are presented as median (95%CI), irAE; immune-related adverse events, E-irAE; endocrine-related irAE, O-irAE; other irAE, EO-irAE; endocrine-related and other irAE, ME-irAE; multiple endocrine-related irAE. COX proportional hazard ratios based on multivariate analysis adjusted for age, sex, history of chemotherapy, history of radiotherapy, and immune checkpoint inhibitors administered.

other hand, participants who developed irAEs showed good treatment response to ICI (Supplementary Fig. 3). Several studies of gastric cancer patients treated with PD-1 inhibitors have reported the development of irAEs and an improvement in the survival rate of gastric cancer patients[25,26]. In this study, the incidence of irAEs was highest in HCC patients, followed by RCC patients, and the proportion of patients with PD was low regardless of the presence or absence of irAEs (Fig. 6C and D). Studies of HCC patients treated with PD-1 inhibitors have reported a correlation between the occurrence of irAEs and clinical benefit[27]. In a meta-analysis of patients with MM, the incidence of irAEs was also reported to be associated with a low HR for OS and PFS[28]. Participants with MM in this study had longer OS than participants with other malignancies. Since this study included all carcinomas, there is a possibility of bias in the analysis of HR for OS due to differences in the observation period

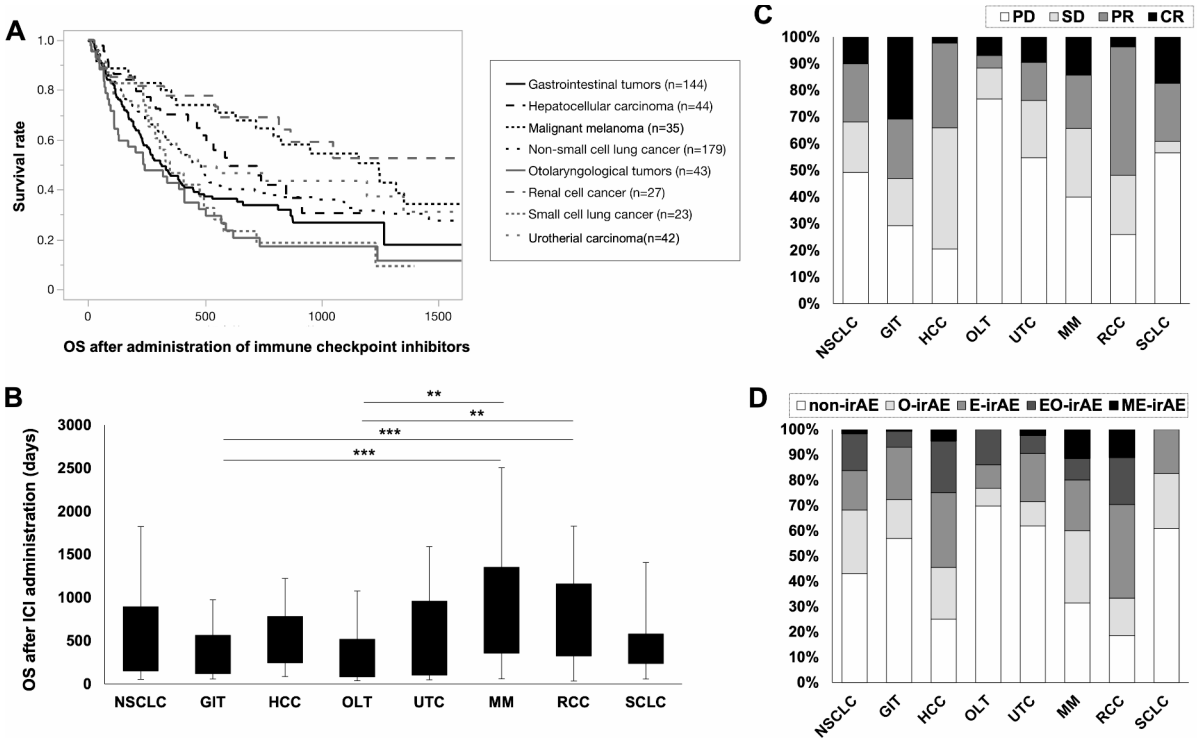

Fig. 6. (**A**) Kaplan-Meier curves for each malignancy by participant were created and log-rank tests were performed. (**B**) Overall survival (OS) for each malignancy by participant. The Kruskal-Wallis test was used for analysis. $^{**}p < 0.005$, $^{***}p < 0.001$. (**C**) Remission rate, (**D**) incidence of each irAE. The remission rate and the incidence of each irAE were analyzed using the chi-square test. NSCLC; non-small cell lung cancer, GIT; gastrointestinal tumor, HCC; hepatocellular carcinoma, OLT; otolaryngological tumor, UTC; urotherial carcinoma, MM; malignant melanoma, RCC; renal cell carcinoma, SCLC; small cell lung cancer, PD; progressive disease, SD; stable disease, PR; partial remission, CR; complete remission.

for each malignancy and the number of cases, and further accumulation of the number of cases is needed for the association between irAE and survival rate for each disease.

Previous chest radiation therapy has been reported to be a risk factor for thyroid-related irAEs and ICI-related interstitial lung disease in lung cancer patients treated with ICIs[29–31]. The combination of radiation therapy and ICI has been suggested to enhance the immune response through cytokine secretion and activation of organ-specific T cells[32–34]. On the other hand, this study found no difference in the incidence of irAEs with or without radiotherapy. There was also no difference in the frequency of irAEs depending on whether or not radiotherapy was used for tumors that could cause direct radiation exposure to the thyroid gland, such as otolaryngological tumors (Supplementary Fig. 4). Previous reports have included analyses of adverse reactions of low CTCAE grade, so there is a possibility that this may have caused the difference in results. In this study, we were unable to include in the analysis the differences between external radiation therapy and internal radiation therapy, as well as the radiation exposure dose and exposure range.

This study has several limitations. First, this is a single-center, retrospective observational study. All participants in this study were Japanese, and the results of this study may not reflect the situation in other countries due to racial differences and differences in treatment strategies in other countries. And, although we made efforts to reduce the impact of bias as much as possible and increase the reliability of the results through strict setting of patient selection criteria, independent data collection methods, and sensitivity analysis such as disease-specific analysis and landmark analysis, there is a possibility that a certain amount of bias remains. Second, in this study, we only included cases where medical treatment was administered as cases of irAE, excluding cases of subclinical hypothyroidism that could be diagnosed based on blood test results as a method of evaluating irAE. On the other hand, there is a possibility that other irAEs may not be recorded in medical records if they are mild, or that cases where tests were not performed in the first place, or cases where skin disorders, gastrointestinal symptoms, etc. are difficult to ascertain without confirmation by the attending physician, may have been included in the study. For this reason, in this study, we analyzed only cases in which additional treatment was required for irAE after ICI administration, or cases in which a change or postponement of ICI was decided due to irAE. Therefore, the frequency of irAE may have been calculated to be low in this study. Thirdly, this study did not analyze the effects of combined anticancer therapy. The analysis of the various carcinomas also resulted in a skewed number of malignancies among the participants. The association between irAEs and treatment outcome may not be consistent across carcinomas and should be examined in more cases in each carcinoma. Finally, although patients without irAE died early or were transferred to other hospitals and

were never diagnosed with irAE, they could have been included if patients with a predisposition to develop irAE had been followed continuously. Patients who did not undergo testing related to irAE were also included in the non-irAE group.

In conclusion, in this study, there was a trend toward higher survival and post-treatment remission rates after ICI administration when Grade 3 or higher irAEs appeared, regardless of type. In addition to this, patients with irAEs in multiple endocrine tissues and patients with irAE in both endocrine and other organs had favorable treatment response after ICI administration. In the landmark analysis of this study, there was no difference in OS between patients who survived for more than one year after ICI administration and those who did not, regardless of whether they had irAEs or not. Therefore, it is important for all clinicians who administer ICI to monitor for immune-related adverse events in the systemic organs, especially the endocrine organs, for at least one year after ICI administration, which may be useful for predicting treatment outcomes.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions
Y.I. designed the study. Y.I., T.K., K.D., H.I., J.S., Y.F., Y.K., M.S., S.N., T.M., and H.K. treated patients and collected data. Y.I. analyzed the data. Y.I., T.K., M.S., S.N., T.M. and H.K contributed to discussion. K.K. supervised the project. Y.I. wrote the manuscript. H.K. reviewed and edited the manuscript.

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Declarations

Competing interests
H.K. has received honoraria for lectures, received scholarship grants, and received research grant from Novo Nordisk Pharma, Sanofi, Eli Lilly, Boehringer Ingelheim, Taisho Pharma, Sumitomo Pharma, Takeda Pharma, Ono Pharma, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Kissei Pharma, MSD, AstraZeneca, Astellas, Novartis, Kowa, Abbott. K.K. has been an advisor to, received honoraria for lectures from, and received scholarship grants from Novo Nordisk Pharma, Sanwa Kagaku, Taisho Pharma, Kowa, Sumitomo Pharma, Mitsubishi Tanabe Pharma, Astellas, Boehringer Ingelheim. S.N. has received honoraria for lectures from Novo Nordisk Pharma and Daiichi Sankyo. All other authors have no conflict of interests.

Additional information
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